How Do We Handle the Anti-HBc Positive Patient? (in Highly Endemic Settings)

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Seropositivity of Hepatitis B Core Antibodies in Hepatitis B Endemic Areas

Since the discovery of hepatitis B core antibodies (anti-HBc) in the 1970s, numerous studies have been conducted to understand their clinical significance.[1] Anti-HBc develops in response to the hepatitis B virus (HBV) infection and typically persists for life, regardless of whether the infection resolves or remains chronic.[2] Therefore, anti-HBc acts as a serum marker for evidence of the HBV infection. In China, as well as in many other countries in the Asia-Pacific region, HBV is endemic, and the prevalence of isolated anti-HBc has been reported to be up to one-third of the population.[3] Thus, it is very common for a practicing clinician in this region to encounter anti-HBc positive patients.

Evaluation of Anti-HBc Positive Subjects

In subjects who are asymptomatic of liver diseases, anti-HBc positivity can be classified into three groups according to the presence or absence of the hepatitis B surface antigen (HBsAg) and the hepatitis B surface antibody (anti-HBs) (Fig. 1). These three groups are: 1) subjects with HBV immunity through natural infection (anti-HBc positive, anti-HBs positive, and HBsAg negative); 2) subjects with chronic HBV infection (HBsAg positive); or, 3) subjects with isolated anti-HBc (anti-HBc positive, anti-HBs negative, and HBsAg negative). It is estimated that three quarters of adults in HBV endemic regions have evidence of previous HBV infection, as shown by isolated anti-HBc. Hence, it is necessary to test the serum for HBsAg and anti-HBs to determine whether the anti-HBc positive subjects suffered from chronic HBV infection—or have recovered from previous HBV infection and therefore have restoration of host immune control of the HBV (Fig. 1). Seropositivity for HBsAg signifies that the subject has chronic HBV infection and should be managed accordingly. If the subject is HBsAg negative and anti-HBs positive, the subject has recovered from a past HBV infection and has immunity against the HBV infection.

Those subjects who are seronegative for both HBsAg and anti-HBs, that is, isolated anti-HBc positivity, could be further classified into three categories. The options for these patients comprise: 1) not administering anti-HB vaccination, 2) administering one dose of anti-HB vaccine and then checking the anti-HBs titers to see whether there is a 'booster' anamnesic response (anti-HBs greater than 10mIU/mL), or 3) administering a complete vaccination series. Thus, whether patients with isolated anti-HBc require vaccination against HBV remains controversial. Further testing for the presence of low-level HBV DNA in the plasma by sensitive polymerase chain reaction (PCR) techniques such as nucleic acid testing will help define whether individual patients with anti-HBc positive, HBsAg negative serologies are in fact harboring 'occult HBV infection' (OBI). The molecular basis of OBI appears to be related to the long-lasting persistence in the nuclei of the hepatocytes of the HBV covalently closed circular DNA (cccDNA), an intermediate form of the virus life cycle that serves as a template for gene transcription.[4]

Clinical Implications and Management of Occult HBV Infection (OBI) in Patients who Anti-HBc Positive

Clinically, seropositive OBI is important in several settings (Table 1). HBV infection may be transmitted by orthotopic liver transplantation if the donor is OBI positive, due to the presence of cccDNA in the hepatocytes.[5] Nucleoside

Abbreviations: anti-HBc, hepatitis B core antibodies; anti-HBs, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus

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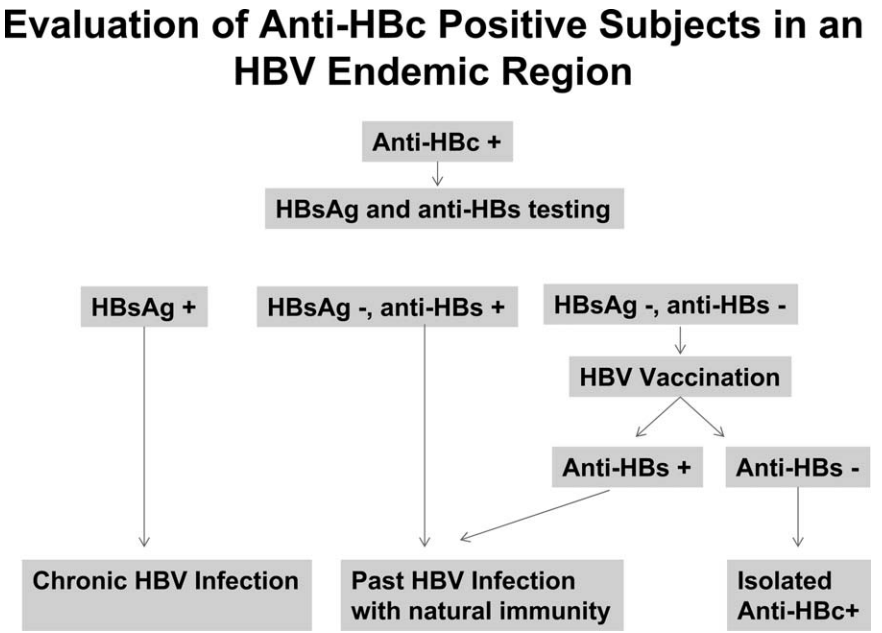

Figure 1 Evaluation of anti-HBc positive subjects in HBV endemic region.

monotherapy with lamivudine, entecavir, or tenofovir (without hepatitis B immunoglobulin) is sufficient to prevent HBV infection in HBsAg negative recipients of anti-HBc positive donor livers.[6] However, further studies are needed to determine whether antiviral prophylaxis can be withdrawn in patients with high-titer anti-HBs after liver transplantation.

HBV reactivation, after intense immunosuppression, occurs more rarely in OBI than in HBsAg positive patients. Hematological malignancies, hematopoietic stem cell transplantation, and therapeutic schedules comprising rituximab appear to be the clinical conditions with the highest risk of OBI reactivation—usually diagnosed when it is followed by the occurrence of a typical acute hepatitis B—whereas it is likely to be underdiagnosed when the clinical sequelae are less severe.[7] The incidence of HBV reactivation and HBV-related hepatitis flares after rituximab-CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone)-based chemotherapy was reported to be 10.4 and 6.4 per 100 person-year, respectively. In addition, severe HBV-related hepatitis (alanine aminotransferase >10-fold of upper limit of normal) occurred in some patients, despite entecavir treatment.[8] Hence, in seropositive OBI patients treated with rituximab-containing chemotherapy or bone marrow transplantation, one should consider the use preemptive anti-HBV nucleos(t)ide analogues. In other immunosuppressive settings, such as use of anti-TNF; chemotherapy for solid tumor careful serial monitoring of the serum HBV DNA level and HBsAg is required to detect significant HBV virological reactivation, with the initiation of nucleos(t)ide analogues when reactivation is observed. Based on viral and biochemical kinetics data, a schedule of monitoring serum HBV DNA and HBsAg at 4-weekly intervals should be adequate to allow for administration of effective nucleos(t)ide analogues to intercept a clinically significant HBV reactivation. In our experience, the detection of HBsAg positivity or an increase in serum HBV DNA > 1 log should be used as criteria for initiating effective anti-HBV nucleos(t)ide analogues.[9] For OBI patients who require indefinite tumor necrosis factor alpha inhibitors, the risk of

TABLE 1 Clinical Management of "Isolated" Anti-HBc Positivity

Clinical Settings	Measures to Be Taken
Transmission of HBV	
Blood transfusion	Nucleic acid testing by PCR
Liver transplantation	Nucleos(t)ide monotherapy is sufficient in preventing HBV infection in anti-HBs negative recipients of anti-HBc positive donor livers
HBV reactivation	
Rituximab-containing chemotherapy or bone marrow transplantation, or when serum hepatitis B DNA monitoring is not feasible for practical reasons	Preemptive use of nucleos(t)ide analogues
Other immunosuppressive settings (e.g., use of anti-tumor necrosis factor, chemotherapy for solid tumor)	4-weekly serial monitoring of serum HBV DNA and HBsAg to detect significant hepatitis B virologic reactivation

HBV reactivation is low. However, one might still choose to initiate prolonged tenofovir or entecavir therapy rather than 4-weekly interval monitoring; the latter might be troublesome and carries the risk of reactivation due to lapses in the surveillance program.[10]

Summary

There is growing evidence that anti-HBc positivity is not a clinically insignificant disease entity. In an HBV endemic area, it is common to encounter anti-HBc positive subjects. In view of the increased use of immuosuppressive agents for the treatment of cancer and organ transplantation, there is increased awareness of the importance of anti-HBc positive occult HBV infection. A proper evaluation of anti-HBc subjects in various clinical settings is essential for good clinical practice in an HBV endemic area. ■

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